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Smell identification in individuals at clinical high risk for schizophrenia

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ABSTRACT

Smell identification deficits exist in schizophrenia, and may be associated with its negative symptoms. Less is known about smell identification and its clinical correlates in individuals at clinical high risk (CHR) for schizophrenia and related psychotic disorders. We examined smell identification, symptoms and IQ in 71 clinical high-risk (CHR) subjects and 36 healthy controls. Smell identification was assessed using both the 40-item University of Pennsylvania Smell Identification Test (UPSIT; Doty, R.L., Shaman, P., Kimmelman, C.P., Dann, M.S., 1984. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. Laryngoscope 94, 176–178) and its extracted 12-item Brief Smell Identification Test (Goudsmit, N., Coleman, E., Seckinger, R.A., Wolitzky, R., Stanford, A.D., Corcoran, C., Goetz, R.R., Malaspina, D., 2003. A brief smell identification test discriminates between deficit and non-deficit schizophrenia. Psychiatry Research 120, 155–164). Smell identification did not significantly differ between CHR subjects and controls. Among CHR subjects, smell identification did not predict schizophrenia ($N=19$; 27%) within 2 years, nor was it associated with negative or positive symptoms. This is the third prospective cohort study to examine smell identification in CHR subjects, and overall, findings are inconclusive, similar to what is found for other disorders in adolescents, such as autism spectrum, attention deficit and anxiety disorders. Smell identification deficit may not have clear utility as a marker of emergent schizophrenia and related psychotic disorders.

1. Introduction

Smell identification deficits (SID) are well documented in subjects with schizophrenia (reviewed by Moberg et al. (2014), in whom they are variably related to negative symptoms (Brewer et al., 1996; Malaspina and Coleman, 2003; Moberg et al., 2006; Ishizuka et al., 2010, but see Moberg et al. (2014) for null association of effect sizes with negative symptoms in meta-analysis). SID are also seen in children and adolescents with psychosis, particularly those with schizophrenia, in whom they are related to negative symptoms and IQ (Corcoran et al., 2005). Less is known about smell identification in youths at clinical high risk (CHR) for psychosis, ascertained on the basis of new or worsening subthreshold (i.e. attenuated) psychotic symptoms (McGlashan et al., 2003). To date, there have been two other prospective studies examining baseline smell identification in at-risk cohorts (Brewer et al., 2003; Woodberry et al., 2010). In the earlier study using the 40-item University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984), Brewer et al. found no difference in smell identification between healthy controls and CHR subjects, though SID did characterize those CHR subjects who later developed schizophrenia (though not psychosis more generally), when accounting for IQ (Brewer et al., 2003). However, questions arose as to the cross-cultural validity of the UPSIT in its entirety, such that later studies used the Brief Smell Identification Test (BSIT; Goudsmit et al., 2003), previously called the Cross-Cultural Smell Identification Test (Doty et al., 1996), which is composed of 12 items (among 40) in the UPSIT that are most familiar across cultures. In the second later prospective study of baseline smell identification in CHR subjects, using the BSIT (Doty et al., 1996; Goudsmit et al., 2003), SID were found in CHR subjects as compared with controls, but did not predict psychosis onset (Woodberry et al., 2010), findings opposite to that found by Brewer et al. (2003) in the earlier study using the UPSIT. Using Sniffin' Sticks (Hummel et al., 1997), we have previously shown equivalent smell identification in a subgroup of our current cohort, i.e. 20 healthy controls and 21 CHR patients, including three who progressed to schizophrenia, who otherwise differed in olfactory

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event-related potentials and odor threshold (Kayser et al., 2013). Herein, we evaluated smell identification in an extended cohort of 71 CHR patients and 36 healthy controls, using both the total score from the UPSIT (Doty et al., 1984), and the sum of the 12 extracted items that constitute the BSIT (Doty et al., 1996; Goudsmit et al., 2003). Percentile scores were used to adjust for age and sex. First, we aimed to replicate the prior finding of relative deficit in smell identification in CHR subjects (Woodberry et al., 2010). Second, we evaluated the predictive value for schizophrenia and related psychotic disorders among CHR subjects of smell identification deficits, using both the UPSIT and its 12-item derived BSIT, given disparate findings in the other prior studies (Brewer et al., 2003; Woodberry et al., 2010). Finally, we examined the clinical correlates of smell identification in CHR subjects, specifically negative symptoms, an association variably observed in schizophrenia (Brewer et al., 1996, Malaspina and Coleman, 2003); Moberg et al., 2006; Corcoran et al., 2005; Ishizuka et al., 2010, but see Moberg et al. (2014) for null association in meta-analysis), and previously in a subgroup of our current cohort (Kayser et al., 2013), although not in other prior studies (Brewer et al., 2003).

2. Methods

2.1. Participants

Subjects at clinical high risk for psychosis (CHR; $n=71$) and healthy control (HC) participants ($n=36$) similar in demographics were participants in the Center of Prevention and Evaluation (COPE), a prodromal research program at New York State Psychiatric Institute at Columbia. Recruitment and ascertainment relied on clinician referrals, Craigslist, the program website, presentations in the community and the mailing of brochures. CHR subjects were help-seeking individuals ages 14–30 who met criteria for the attenuated positive symptom syndrome, as assessed with the Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2003). Exclusion criteria included any major medical or neurological disorder, IQ less than 70, significant risk of harm to self and others, an inability to speak English, and/or "prodromal" symptoms occurring solely in the context of substance intoxication or withdrawal, or which were better accounted for by another Axis I diagnosis, such as mood disorder. Additional exclusion criteria for healthy controls included any current Axis I disorder within the past 2 years, as assessed by structured diagnostic interview, and any personal or familial (first degree relative) history of psychosis. CHR subjects also had the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID; First et al., 2002) to assess comorbidity. Use of antipsychotics and/or antidepressants was ascertained by self-report, as was any use of substances of abuse, including tobacco and marijuana. All CHR patients were offered treatment, which comprised individual psychotherapy and targeted pharmacotherapy (i.e. anxiolytics for anxiety, antidepressants for depressed mood).

Table 1
Sample characteristics.

Characteristic	Healthy controls ($n=36$)	CHR converters ($n=19$)	CHR nonconverters ($n=52$)
Demographics			
Male (%)	58	90	69
Caucasian (%)	47	32	52
Age in years, mean (S.D.)	21.7 (4.6)	19.4 (3.2)	19.3 (3.8)
Full scale IQ, mean (S.D.)	111.1 (12.3)	109.4 (15.1)	107.5 (17.6)
Clinical features			
Positive symptoms, mean (S.D.)*	1.0 (1.2)	14.5 (4.7)	12.2 (4.6)
Negative symptoms, mean (S.D.)*	1.1 (1.5)	15.1 (6.1)	12.4 (6.4)
GAF, mean (S.D.)*	83.9 (7.7)	42.5 (4.5)	46.2 (8.1)
Antipsychotic use (%)	0	11	14
Antidepressant use (%)	0	11	25
Marijuana use (%)	17	16	19
Smell identification			
UPSIT % score, mean (S.D.)	19.0 (20.9)	14.6 (16.4)	18.2 (18.6)
BSIT % score, mean (S.D.)	28.9 (29.1)	23.6 (33.4)	28.9 (29.3)

* ANOVA, overall model $F_{2,102}=116.5$ for positive symptoms, $F_{2,102}=63.6$ for negative symptoms, and $F_{2,102}=315.3$ for GAF, all p's <0.001; for all corresponding post-hoc Tukey tests: converters > controls ($p<0.001$), nonconverters > controls ($p<0.001$) and converters = nonconverters (n.s.)

2.2. Assessments

The Structured Interview for Prodromal Syndromes/ Scale of Prodromal Symptoms (SIPS/SOPS; McGlashan et al., 2003) was used to assess positive and negative symptoms, and administered prospectively every three months to determine transition to schizophrenia and related psychotic disorders among CHR subjects. Smell identification was assessed at baseline using the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984), a standardized 40-item forced choice test of smell identification in which stimuli are embedded in "scratch and sniff" microcapsules fixed on strips at the bottom of each page. Subjects scratch and sniff each microcapsule and then pick one of four response alternatives that best describe the odor. Smell identification was identified as the total percentile score for both the UPSIT and its 12 extracted items that constitute the Cross Cultural Smell Identification Test (CC-SIT; Doty et al., 1996), also known as the Brief Smell Identification Test (BSIT) (Goudsmit et al., 2003). These 12 extracted items from the UPSIT include six food-related and six nonfood-related odorants familiar to persons not only from North American and European countries, but also from South American and Asian cultures (Doty et al., 1996), specifically: banana, chocolate, cinnamon, lemon, onion, pineapple, paint thinner, gasoline, rose, soap, smoke and turpentine. Full-scale IQ was measured using the 3rd edition of the Wechsler Adult Intelligence Scale (WAIS III; Wechsler, 1997).

2.3. Statistical analysis

ANOVA was used to test group differences among healthy controls and CHR subjects, stratified by transition to schizophrenia and related psychotic disorders within 2 years (i.e. "converters" and "nonconverters"), in terms of demographics, IQ, clinical variables (positive and negative symptoms, global function), and smell identification (percentile scores for both the UPSIT and the extracted BSIT). Post-hoc Tukey tests were used for pairwise comparisons. It was hypothesized that CHR converters would have worse smell identification than both CHR nonconverters and controls. Post-hoc analyses were conducted to test any group differences for individual items on the BSIT. χ^2 analyses were used to evaluate potential group differences in gender and ethnicity. Any demographic variables (i.e. age) that had a significant association with smell identification percentile scores or group were then included as covariates in partial correlational analyses of smell identification and clinical variables.

3. Results

There were 36 healthy controls and 71 CHR subjects, among whom 19 (27%) CHR subjects developed threshold psychosis (>90% with schizophrenia or schizoaffective diagnosis) over 2-year follow-up (i.e. "converters"). The cohort was in its late teens and early twenties, primarily male, and ethnically diverse (Table 1). IQ was similar across groups (Table 1). As expected, positive and negative symptoms, and impairment in global function were evident among CHR subjects; however, they were not significantly more severe among CHR converters (Table 1). Among CHR subjects, 18% endorsed current use of marijuana and none endorsed tobacco use. Eight percent of CHR subjects were taking antipsychotics and 14% antidepressants. Rates of comorbid diagnosis were 37% for depressive disorders and less than 10% each for anxiety disorders, autism spectrum, ADHD and eating disorders. While demographic characteristics were not significantly different among groups, healthy controls were about 2 years older on average than CHR subjects and had a numerically larger proportion of women (42% vs. 25%), hence, percentile scores specific to age and gender were used for assessment of smell identification.

Converters had lower percentile scores than both controls and nonconverters for both the UPSIT (14.6 vs. 19.0 in controls, 18.2 in

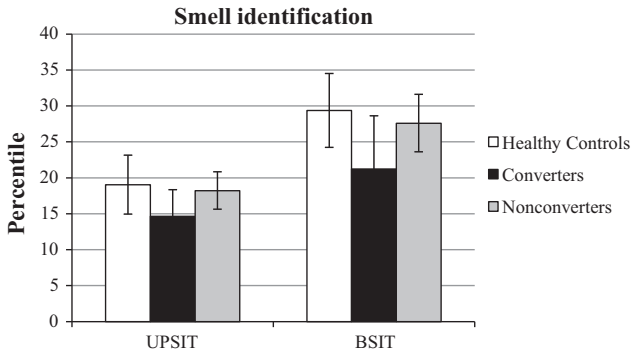

Fig. 1. Smell identification in the cohort. Mean scores for healthy controls (white), converters (black) and nonconverters (gray) for UPSIT and BSIT percentile scores. Error bars represent the standard error of the mean. ANOVA is used for group comparisons.

nonconverters) and the BSIT (23.6 vs. 28.9 in both controls and nonconverters), but these differences were not statistically significant given relatively large standard deviations of $>15\%$ (Fig. 1). Of note, a similar pattern was seen for raw scores for the UPSIT and BSIT (data not shown). Estimated effect sizes for differences by psychosis transition were Cohen's $d=-0.20$ for the USPIT and Cohen's $d=-0.17$ for the BSIT. Post-hoc analyses by sex showed no difference in percentile scores among controls, converters and non-converters (all p's >0.10). Individual BSIT items did not differ by group (all p's >0.20). Among CHR subjects, smell identification was unrelated to the use of marijuana, the prescription of antipsychotics or antidepressants or the presence of comorbid depressive or anxiety disorder (all p's >0.10). Adjusting for age in partial correlation analyses, negative symptoms were unrelated to both UPSIT ($r=-0.05$, $p=0.65$) and BSIT ($r=0.04$, $p=0.72$) percentile scores. Likewise, in exploratory partial correlation analyses, positive symptoms were unrelated to both UPSIT ($r=0.01$, $p=0.95$) and BSIT ($r=0.19$, $p=0.12$) percentile scores, as was true for IQ and global function (all p's >0.10).

Overall, smell identification had no significant relationship in CHR subjects with later development of schizophrenia and related psychotic disorders or with concurrent clinical features.

4. Discussion

In the current study, smell identification did not differ between clinical high-risk patients and healthy controls ascertained from the same source population in the New York metropolitan area and recruited primarily via the Internet. Further, while mean smell identification percentile scores were lower in CHR patients who later developed schizophrenia and related psychotic disorders, as compared with both healthy controls and CHR patients who did not develop psychosis, the variance was such that these differences were not statistically significant. Finally, smell identification bore no association in at-risk patients with IQ, symptoms (positive or negative) or function. Smell identification was assessed as percentile scores adjusting for age and gender using both the UPSIT and extracted items that constitute the more culturally valid BSIT.

The lack of difference in smell identification in CHR subjects relative to healthy controls is consistent with an earlier study using the UPSIT in Australia (Brewer et al., 2003), but not with a more recent study in the United States using the BSIT (Woodberry et al., 2010). Disparate findings for group differences among studies may be explained primarily by ascertainment, as all three studies had similar sample sizes (Brewer: 81 CHR, 31 HC; Woodberry: 73 CHR, 34 HC; current study: 71 CHR, 36 HC). In the current study, healthy controls were primarily recruited via Craigslist, and had an average IQ comparable to CHR subjects, in contrast to both prior studies, i.e. 109.4 vs. 102.7, $p<0.05$ (Woodberry et al., 2010). Of note, our healthy controls had mean percentile scores below the expected value of 50%, based on previously published norms in Philadelphia. This may reflect differential ascertainment strategies (i.e. our use of Craigslist) and characteristics associated with participation in a time-intensive research study, which may obscure a potential deficit in the CHR subjects with whom they are compared. This may also explain our prior finding of equivalent smell identification between CHR patients and controls in a subgroup of our current cohort (Kayser et al., 2013), who were assessed with Sniffin' Sticks (Hummel et al., 1997), which is in contrast to a cross-sectional study of CHR subjects using the same method (Kamath et al., 2013).

Our lack of statistically significant difference in smell identification among those at-risk subjects who later developed schizophrenia may be an issue of statistical power, especially in the context of large variance in performance within groups. The one study that found a significant association of smell identification with outcome had a transition rate to psychosis of 37% (Brewer et al., 2003), higher than our transition rate of 27%, and the 19% observed in the other study that did not find a significant difference by psychosis outcome (Woodberry et al., 2010). Given estimated small effect sizes (Cohen's $d=-0.20$ and -0.17 for the UPSIT and BSIT, respectively), a sample size greater than 600 would be required to detect a significant difference in smell identification between those at-risk individuals who later make the transition to psychosis, and those who do not.

In the current study, smell identification was unrelated to symptoms, similar to the one other prior study that examined clinical correlates of smell identification in CHR subjects (Brewer et al., 2003), but in contrast to our prior study in a subgroup of the current cohort, in which negative symptoms were associated with worse Sniffin' Sticks odor identification and detection, and with amplitude reductions in olfactory ERP's (Kayser et al., 2013). Further study in larger cohorts will clarify the relationship of negative symptoms to olfactory function in CHR subjects, to determine if the same association exists as has been variably observed in schizophrenia (Brewer et al., 1996; Malaspina and Coleman, 2003; Moberg et al., 2006; Ishizuka et al., 2010, but see Moberg et al. (2014) for null association of negative symptoms with effect sizes in meta-analysis).

Contextualizing our findings within the small extant literature on smell identification in CHR subjects, it appears that there is not a strong signal of deficit in smell identification in clinical risk states for schizophrenia. A meta-analysis of studies suggests that the large variance in their effect sizes may be related to the effects of moderator variables, and different strategies for ascertainment of both CHR subjects and controls (Moberg et al., 2014). Of note, a pattern of mixed results for SID is evident across many psychiatric disorders in children and adolescents, including attention deficit disorder, autism spectrum disorders, obsessive compulsive disorder and other anxiety disorders (reviewed by Schecklmann et al. (2013), many of which are comorbid diagnoses observed in CHR cohorts, including in the current study (also reviewed by Mazzoni et al. (2009). Of note, our study's main limitations are its size and the relatively low smell identification ability among community-ascertained controls.

Although the diagnostic outcome was primarily schizophrenia (and schizoaffective disorder) among CHR converters in the current study, we did not replicate the findings of Brewer et al. (2003) that SID is predictive of schizophrenia outcome. While SID may not be a reliable indicator of later schizophrenia outcome in CHR subjects, it may instead be an excellent endophenotype for the schizophrenia spectrum, as is supported by findings of SID in

schizotypy, unaffected family members and genetic high-risk subjects (Moberg et al., 2014). Future studies in large CHR cohorts, similarly attentive to diagnosis, ascertainment and potential moderating factors (Moberg et al., 2014), will inform the utility of SID as a risk biomarker for schizophrenia, which may also resolve some of the debate in the field as to the relevance of SID in risk populations (Cohen et al., 2012; Turetsky et al., 2012). The examination of SID in a larger cohort could also allow closer examination of gender differences in olfactory function (Malaspina et al., 2012) in CHR subjects. Importantly, other indices of olfactory function, such as olfactory event-related potentials (Turetsky et al., 2003) or odor detection thresholds may hold more promise for psychosis prediction in risk cohorts (Kayser et al., 2013), while also adding to our understanding of the neural mechanisms of psychosis onset. Of note, in a subgroup of the current cohort, the three CHR converters (of 21 CHR patients studied) had marked reductions in amplitude of baseline olfactory N1 and P2: event-related potentials (ERP's) time-locked to onset of odor stimuli that index the neuronal activity underlying the sequence of olfactory processing (Kayser et al., 2013). Biophysical measures of basic sensory processing (auditory, olfactory and perhaps visual) may hold more promise as biomarkers of emergent schizophrenia than behavioral measures as they provide sensitive and reliable measures of abnormal neural function (Luck et al., 2011).

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